REMARKS

Claims 1-13, and 16, all of the pending claims in this application, are rejected in the Office Action dated July 11, 2007. Claim 1 has been amended to more clearly define the claimed tetrahydroquinoline derivatives of Formula I. Claims 2, 3, and 8 have been cancelled and claims 4, 5, and 9 have been amended to merely maintain proper dependency. Support for the amendments in claim 1 can be found on page 5, lines 4 to 16, and on pages 27 to 56 (examples 1 to 50) of the specification.

Applicants respectfully request entry of the above amendments and reconsideration of the claims.

Claims are Not Anticipated

Claims 1-13, and 16 are rejected under 35 U.S.C. §102(e) as being allegedly anticipated by Van Straten et al I (PCT Int. Appl. WO 20030004028) and by Van Straten et al II (US 2004/0236109). According to the Examiner, numerous species disclosed in Van Straten et al meet the limitations of the instant claims. The Examiner further provides examples of the allegedly anticipating disclosure in Van Straten et al (I and II), such as Example 65, page 53 where R^6 is heterocycloalkyl, R^1 is methyl, R^2 is methyl, R^4 and R^5 are H (CAPLUS RN 487064-92-6), or where R^6 is an heteroaryl (CAPLUS RN 487064-46-0), or where R^6 is a phenyl (CAPLUS RN 487064-30-2).

In response Applicants submit that the claimed tetrahydroquinoline derivatives of formula I require that R^4 and R^5 cannot both be H as in the cited references. Further, the proviso in claim 1 with respect to these substituents specifically requires that "if R^4 is H, R^5 is not OH or (1-4C)alkoxy." Thus if R^4 is a hydrogen then R^5 is R^7, a radical selected from the group as recited in claim 1 and which group does not include hydrogen. In fact, R^7 is different than any of the possible substituents on positions 5, 7, or 8 of the benzene ring of the bicyclic quinoline core disclosed in Van Straten et al (I and II). Therefore, the claimed tetrahydroquinoline derivatives of formula I are clearly distinct from the compounds disclosed in Van Straten et al (I and II). Moreover, R^6 as in amended claim 1 does not include a heterocycloalkyl and thus the compound in Van Straten et al (I and II) referred to above as CAPLUS RN 487064-92-6, is significantly

different from the claimed tetrahydroquinoline derivatives of formula I, and therefore does not anticipate the claimed invention for this additional reason. Accordingly, Applicants submit that claims 1-13, and 16 are not anticipated by Van Straten et al (I and II) and respectfully request withdrawal of the rejection of claims 1-13, and 16 under 35 U.S.C. §102(e).

Claims are Enabled.

Claims 1-13 are rejected under 35 U.S.C. §112, first paragraph, because, according to the Examiner, the specification, while enabling for certain compounds, does not reasonably provide enablement for the protracted list of compounds claimed. The Examiner asserts that the claims are very broad encompassing a variety of heterocycles (mainly R^4 and R^5), bearing multiple substitutions. Further, the Examiner asserts that while a vast array of anilines are commercially available for the Skraup reaction, the substituents R^4 and R^5 apparently have enormous permutations. According to the Examiner, the Skraup reaction has been known to be sensitive to substituents on the starting aniline. In addition, the Examiner asserts that the requirement for activity at the FSH receptor provides no further guidance. According to the Examiner the only available information regarding the claimed compounds is that these can be an agonist, antagonist or both for the FSH receptor. Further, a single compound cannot be both an agonist and an antagonist according to the Examiner. Moreover, in view of Van Straten et al.; Journal of Medicinal Chemistry **2005**, 48, 1697-1700, stating that "aromatic substituents in position 6 (R^6) are preferred ..." and "space is limited because introduction of an extra t-butyl group in 11 led to a drop in potency" the Examiner asserts that there is an apparent size constraint on substituents. According to the Examiner, one could not make/use the claimed invention.

In response applicants submit that for each of the possible substituents for R^4 and R^5 of the claimed tetrahydroquinoline derivatives of formula I at least one representative example is provided in the currently pending application. The claimed tetrahydroquinoline derivatives of formula I in independent claim 1, as amended (incorporating claims 2 and 3 into claim 1), are clearly supported by the examples in the

specification. Each one example provides a method of preparing the claimed tetrahydroquinoline derivative. Moreover, the specification on pages 9-20 provides a detailed description of methods for preparing the claimed tetrahydroquinoline derivatives of formula I. In addition, the specification provides in Example 51 methods of determining the activity (whether it be as an agonist or antagonist) for each of the disclosed examples. In fact, the specification on page 57 describes that "compounds of all examples exhibited an $EC_{50}(IC_{50})$ value of less than 10^{-5}M in either an agonistic or antagonistic assay set-up or both. The compounds of examples 5-8, 10-14, 16, 18-20, 33-35, 37, 38, 41, and 45-50 showed an EC_{50} of less than 10^{-7}M in at least one of the assays." In addition, with respect to the Examiner's statement that some compounds show both agonist and antagonist activity, Applicants submit that some of the claimed compounds, as indicated in the specification, indeed show both agonist and antagonist activity in the assays described in example 51 of the specification. Applicants thus submit that some compounds can interact with the FSH-receptor and have both agonist and antagonist activity. The Examiner has provided no evidence to question this experimental evidence discussed in the currently pending application. In addition, Applicants note that some ligands for certain G-protein coupled receptors (the FSH receptor is a G-protein coupled receptor) have been observed to have both agonist and antagonist activity. Therefore, the observation that some of the claimed tetrahydroquinoline derivatives are both agonist and antagonist is not a contradiction as suggested by the Examiner's comments, which comments are unfounded and contrary to the observed experimental results. Thus, Applicants submit that the specification provides an enabling disclosure for the claimed tetrahydroquinoline derivatives of formula I describing at least one synthetic method for such derivative as well as showing activity with respect to the FSH receptor. For these reasons applicants submit that the skilled artisan reading the disclosure of the currently pending application would know how to make and/or use the claimed invention. Accordingly, Applicants submit that claims 1-13 are clearly enabled by the specification as filed and respectfully request withdrawal of the rejection of claims 1-13 under 35 U.S.C. §112, first paragraph.

Claim 16 is rejected under 35 U.S.C. §112, first paragraph for failing to comply with the enablement requirement. The Examiner asserts that while the claim is directed to a method of fertility regulation there is no nexus between the claimed compounds and methods of fertility regulation. According to the Examiner the FSH receptor, a G-protein coupled receptor with a vast number of binding sites and conformations, may be associated with distinct physiological outcomes depending on the binding site that is activated. In view of this statement the Examiner refers to Guo, Tao; Expert Opinion on Therapeutic Patents 2005, 15(11), 1555-1564, stating that only in the clinic will the question of whether a small molecule FSH receptor modulators will be successful as fertility agents be answered. According to the Examiner there is no successful use of the compounds in the claimed method in an animal model and no clear correlation between antagonism of this receptor and a therapeutic outcome. The Examiner also refers to a passage in the Kenakin et al. article, "The ligand paradox between affinity and efficacy: can you be there and not make a difference", TRENDS in Pharmacological Sciences, 2002, 23, 275-280", to allegedly show that in the present case "we have exactly this situation, namely a ligand with affinity, but not known function, which as Kenakin et al. concluded "...the discovery of macro-affinity of a ligand for a receptor should be considered only a starting point for the optimal exploitation of a drug for therapeutic utility."

In response, applicants submit that the claimed tetrahydroquinoline derivates of formula I are shown to be ligands (either as agonist or antagonist) for the FSH receptor, as demonstrated in Example 51 of the specification of the currently pending application. The assay determining efficacy of the claimed tetrahydroquinoline derivatives as either an agonist or antagonist for the FSH receptor relies on cAMP accumulation. Activation of the FSH receptor with FSH has previously been correlated with cAMP accumulation. Further, FSH receptor activation with FSH is a well described pathway in regulating fertility. Thus, applicants submit there is a clear nexus between the observed activity of the claimed tetrahydroquinoline derivatives of formula I and a method of regulating fertility.

In addition, Applicants submit that the Examiner's statement citing Tao Guo is taken out of context. Guo does not dispute that activation or inhibition of the FSH receptor by small molecules, to which class of compounds the claimed tetrahydroquinoline derivatives of formula I belong and which have been shown to have acceptable agonist and/or antagonist activity, provides no nexus with respect to regulating fertility. Indeed, Guo indicates a correlation between antagonism of the FSH receptor and a therapeutic outcome, i.e., fertility regulation. In this regard, the Examiner's attention is directed to Guo, page 1562, second column, wherein it states *inter alia*:

> ...Most importantly, FSHR antagonists, such as compounds 24 and 25, have been demonstrated to inhibit oestradiol synthesis and ovulation in female rats [62-64], bolstering confidence that small molecule FSHR antagonist could be developed into novel, non-steroidal contraceptives in women....

Accordingly, in contrast to the Examiner's statement that "There is no successful use of these compounds in an animal model and no clear correlation between antagonism of this receptor and a therapeutic outcome, thus undue experimentation would be required", Guo indicates that compounds functioning as FSHR antagonists have been shown in animals to possess therapeutic utility.

The statement by Guo that "only in the clinic will the question of whether small molecule LHR and FSH modulators will be successful as fertility-regulating agents be answered," is directed to the commercial development of one or a few of such small molecules which may actually be used in the treatment of patients. However, a variety of factors not necessarily related to efficacy or ability to modulate fertility by such compound are considered in order to arrive at such [commercially] successful small molecule. In other words considerations such as for example lowest degree of potential side effects or the level of cross reactivity may be additional factors that are considered. Applicants submit that these considerations are unrelated as to whether or not the claimed tetrahydroquinoline derivative of formula I can be used to regulate fertility.

Indeed, it is duly noted that clinical studies/FDA approval, is not a prerequisite for finding a compound useful within the meaning of the patent laws. *Scott v. Finney*, 34 F. 3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994).

With respect to the Examiner's statement pertaining to the Kekankin et al. article, the fact remains that while Kenakin et al. discuss in general that ligands will produce a bias in the conformation of the receptor ensemble, Kenakin et al., in the passage cited by the Examiner, states nothing whatsoever regarding the therapeutic utility of FSH antagonists, in particular, the presently claimed compounds. As stated above, Guo clearly indicates a correlation between antagonism of the FSH receptor by compounds functioning as FSH antagonists and a therapeutic outcome.

For all of the above reasons, Applicants submit there is a nexus between the claimed compounds and methods of fertility regulation as in claim 16. Accordingly, Applicants submit that claim 16 is clearly enabled by the specification as filed and respectfully request withdrawal of the rejection of claim 16 under 35 U.S.C. §112, first paragraph.

Double Patenting Rejection.

Claims 1-13, and 16 are provisionally rejected on the ground of non-statutory obviousness-type double patenting as being unpatentable over claims 1-9 of copending application 10/482,707 and over claims 1-9 of copending application 10/540,335. According to the Examiner, although the wording of these allegedly conflicting claims is not identical they are not patentably distinct because there is substantial overlap in scope of the claims. The Examiner notes that the wording is only slightly different and that the '707 application is broader and the '335 application is narrower.

In response to the obviousness-type double patenting rejection of claims 1-13, and 16 over claims 1-9 of co-pending application 10/482,707 ("the '707 application"), Applicants submit that the claimed tetrahydroquinoline derivatives of formula I are very different from the compounds in claims 1-9 of the co-pending '707 application. In the currently claimed invention the tetrahydroquinoline derivatives of formula I require that **both** positions 5 and 7 of the benzene ring of the bicyclic tetrahydroquinoline are

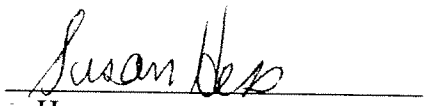
substituted with R^4 and R^5 respectively, whereas the compounds in the '707 only require **one** substituent on any one of positions 5, 7 and 8 of the same benzene ring. If however one of these subtituents in the claimed invention is hydrogen, R^4 may be H, the other substituent (R^5) is selected from amino, (di)(1-4C)alkylamino, (2-5C)heteroarylcarbonylamino, (2-5C)heteroarylcarbonyloxy, R^8-(2-4C)alkoxy, R^9-methylamino or R^9-methoxy, all of which differ substantially from the possible substituents disclosed in the '707 application for this position. There is no teaching or suggestion in the '707 application that the 5, 7, and 8 positions of the benzene ring of the tetrahydroquinoline compound disclosed therein can be substituted as in the claimed invention. Accordingly, Applicants submit that, in contrast to the Examiner's assertions, there is no overlap between the claimed compounds and that the compounds in claims 1-9 of the co-pending '707 application nor does the disclosure in the '707 application teach or suggest the claimed tetrahydroquinoline derivatives. For this reason Applicants respectfully request withdrawal of the provisional rejection of claims 1-13 and 16 under the non-statutory doctrine of obviousness type double patenting.

In response to the obviousness-type double patenting rejection of claims 1-13, and 16 over claims 1-9 of co-pending application 10/540,335, Applicants defer responding to the rejection until such time as any of the above claims is allowed at which time applicants, although disagreeing with the Examiner's assertions, intend to submit a proper Terminal Disclaimer.

In view of the above amendment, Applicants believes the pending application is in condition for allowance. If the Examiner believes a telephone conference would be of value, he is requested to call the undersigned at the number listed below. Applicants respectfully request the issuance of a timely Notice of Allowance in the case.

Dated: November 13, 2007

Respectfully submitted,

By 
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